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Neoadjuvant chemotherapy for muscle invasive bladder cancer: A nationwide investigation on survival

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Abstract

Objectives

Randomised controlled trials (RCTs) have investigated the use of neoadjuvant chemotherapy (NAC) and its effect on survival patients with non-metastatic muscle-invasive bladder cancer (MIBC). However, these RCTs have limited external validity and generalisability, and therefore the current study aims to use real world evidence in the form of observational data to identify the effect that NAC may have on survival, compared to the use of radical cystectomy (RC) alone.

Materials and Methods

The study cohort (consisting of 944 patients) was selected as a target trial from the Bladder Cancer Data Base Sweden (BladderBaSe). We calculated 5-year survival and risk of bladder cancer (BC)-specific and overall death by Cox proportional hazard models for the study cohort and a propensity score (PS) matched cohort.

Results

Those who had received NAC had higher 5-year survival proportions and decreased risk of both overall and BC specific death (HR=0.71 95%CI: 0.52-0.97 and HR=0.67, 95%CI: 0.48-0.94) respectively, as compared to patients who did not receive NAC. The PS matched cohort showed similar estimates but with larger statistical uncertainty (Overall death: HR=0.76, 95%CI: 0.53-1.09 and BC-specific death: HR=0.73, 95%CI: 0.50-1.07).

Conclusion

Results from the current observational study found similar point estimates for 5-year survival and of relative risks as previous studies. However, our results based on real world evidence had larger statistical variability, resulting in a non-statistically significant effect of NAC on survival. Future studies with detailed validated data can be used to further investigate the effect of NAC in narrower patient groups.

Keywords/phrases: Muscle invasive bladder cancer, neoadjuvant chemotherapy, radical cystectomy, survival

Introduction

In Europe the recommended gold standard treatment for patients with muscle invasive bladder cancer (MIBC) is radical cystectomy (RC) with pelvic lymph node dissection and where eligible, neoadjuvant chemotherapy (NAC) [1]. More than 50% of patients with MIBC, but not metastatic disease, do not survive past 5 years post-cystectomy, with most dying of distant metastases [2].

Patients who are eligible to receive NAC, will normally receive a platinum-based chemotherapy such as cisplatin combination chemotherapy [1]. The European Association of Urology (EAU) guidelines recommend that these patients are those with MIBC (T2-T4a, cN0 M0) and good renal function [1].

Several randomised controlled trials (RCTs) have aimed to identify the use of NAC and its effect on survival. The results have been varied, with some stating a paucity in survival improvement [3,4] and others showing the contrary [5–7]. Despite these discrepancies, a systematic analysis encompassing 11 RCTs, found an overall significant survival benefit for patients receiving NAC, in particular when a cisplatin-based combination chemotherapy regime was used [8].

Whilst they each have their own distinct roles in research, RCTs and observational studies can be used to complement each other [9]. The benefit of performing a study with observational data versus an RCT, is that it can provide insight into the treatment options available and their benefits, whilst maintaining good external validity [10]. The results produced by RCTs may not be generalizable to a wider population, therefore they can be

strengthened by the results from observational data. To ensure generalisability whilst considering the importance of RCTs, we aimed to investigate the effect of NAC on mortality among patients undergoing RC using real world data from BladderBaSe Sweden in the form of a target trial.

Material and Methods

Data Source

The Bladder Cancer Data Base Sweden (BladderBaSe) was created in 2015. It links information from the Swedish National Register of Urinary Bladder Cancer (SNRUBC) from 1997 to 2014, with a number of national health care and demographic registers through the personal identification numbers [11,12]. At present, 38,658 patients are registered in BladderBaSe, which captures about 97% of all bladder cancers (BCs) in Sweden during that time. As BladderBaSe is also linked to other registers such as the National Cancer Register and the Register of Total Population and Population Changes [13], information on patients' comorbidities, socioeconomics, re-admissions, adverse effects and causes of deaths [14] is available.

Data from the National Patient Register on discharge diagnoses from hospital admissions up to ten years prior to the date of BC diagnosis was used to calculate the Charlson Comorbidity Index (CCI), which was categorised into four groups: no comorbidity, 1, 2, and ≥ 3 comorbidities [15,16]. Data on educational level was retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies at Statistics Sweden and categorised into three groups: ≤ 9 years, 10–12 years, and ≥ 13 years of education, corresponding to low, intermediate and high education level [17].

Study Cohort Population

A target trial was emulated from BladderBaSe through which we selected all BC patients who had received RC as their primary treatment between 2008 and 2014 with clinical T2-T4, N0/NX and M0/MX disease, no known renal disease and aged 75 years or below (n=944). Figure 1 depicts the process through which these patients were selected as well as the clinical T-stage distribution at each step. Data on whether these patients were given NAC of any type prior to their RC was extracted as the exposure variable. The primary outcome was determined as death either from all causes, or from BC specifically. Date and cause of death were obtained from the Cause of Death Register and death from BC was defined as International Classification of Disease (ICD)-10 code C67. 2008 was chosen as the first year to include patients in the cohort as this is when the EAU guidelines first recommended NAC as a treatment for patients with MIBC [18].

Limited lymph node dissections are generally performed in Sweden; therefore, it can be assumed that the majority of the patients were treated this way. For those given NAC, the decision was made by the treating urologist after consent by the patient whilst using guidance from the National Guidelines. The decision to give adjuvant chemotherapy was also at the discretion of the treating urologist and patient.

Propensity score matching

The study cohort was used to carry out propensity score (PS) matching for NAC using a caliper of 0.1. The cohort was 1:1 matched using the following factors: smoking history, CCI, age at diagnosis, education level, marital status, sex, health care region, hospital type, year of cystectomy, clinical tumour stage and clinical N stage. Smoking history was assessed based on the diagnosis of any combination of: Chronic obstructive pulmonary disease (COPD)

(ICD-10: J44), emphysema (J43), respiratory conditions due to inhalation of chemicals, gases, fumes and vapours (J684) and acute bronchiolitis (J219). Complications within 90 days from radical cystectomy were determined based on the surgical and diagnostic codes outlined in supplementary table 1.

Statistical Analysis

Cox proportional hazards regression analysis was carried out on both the study and PS matched cohorts separately to produce hazard ratios as a measure of relative risks of overall or BC specific death. Start date of the study was date of surgery and last date of the study was date of death, emigration, or December 31, 2014, whichever occurred first. Time in years from diagnosis was used as the timescale. The assumption of proportional hazards was tested using Schoenfeld residuals when adjusted for all confounders and was found valid for both overall and BC specific death. All models for the study cohort were adjusted for smoking history, CCI, age at diagnosis, education level, marital status, gender, complications, adjuvant chemotherapy, health care region, hospital type, year of cystectomy and clinical tumour stage. Models for the PS matched cohort were adjusted for complications, adjuvant chemotherapy and clinical M stage. A sensitivity analysis was implemented for the study cohort by excluding those who had a survival time of less than one year in an attempt to ensure patients underwent a cystectomy with curative intent. A further sensitivity analysis was also executed by excluding those who received adjuvant chemotherapy. Next, both cohorts were stratified by clinical T-stage and subsequent interaction tests were carried out by adding the product of NAC and T stage into the model.

Moreover, 5-year survival estimates for overall and cancer-specific survival in both cohorts were calculated using Kaplan-Meier curves and were stratified by NAC use. Finally,

cumulative incidence functions using competing risk models were created to compare stratified T stage and NAC groups in both cohorts.

All data management was performed with STATA MP/2 version 14 (StataCorp LP, College Station, Texas), whilst all statistical analyses were performed with STATA/IC 12.1 (Texas, USA) and R 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The mean age of the study cohort was 66.78 (IQR=9.30) (Table 1). Those who received NAC were slightly younger compared to those who did not (mean age of 67 vs 65). Most patients did not have any comorbidities. However, fewer of those who received NAC had three or more comorbidities compared to those who did not receive NAC (2% versus 4% respectively). Overall, there were more T2 tumours (86%) than T3 or T4 (9% and 4% respectively). In total 30% of all patients received NAC, whilst 8% received adjuvant chemotherapy.

Table 2 shows the relative risks for all-cause and BC-specific death for patients treated with NAC as compared to no NAC in the study cohort. Overall, there was a median follow up time of 1.81 years (IQR: 3.17 years, 25th percentile: 0.79 years and 75th percentile: 3.96 years). Those who received NAC were at a decreased risk of all-cause death compared to those who did not (HR: 0.71, 95% CI: 0.52-0.97). This decreased risk was also seen for BC-specific death (HR: 0.67 (95% CI: 0.48-0.94). Upon excluding those with a follow-up time <1 year, the results weakened [HR: 0.86 (95% CI: 0.55-1.35) for all-cause death and HR: 0.85 (95% CI: 0.52-1.40) for BC-specific death]. However, excluding those who received adjuvant chemotherapy did not alter the results substantially (HR for BC specific death: 0.68, 95% CI:

0.47-0.96). An additional sensitivity analysis by removing those patients with MX tumours did not significantly change the result.

[Tables 1 and 2 near here]

The PS matched cohort consisted of 432 patients equally distributed between the NAC and no NAC groups (Table 1). The majority of variables were well matched, with a relatively equal distribution across the two arms. The worst matched variable was health care region. Upon repeating the analyses from Table 2 (i.e. the study cohort) using the PS matched cohort, the trend of the results remained (Table 3). Patients who received NAC had a decreased risk of all-cause death (HR: 0.76, 95% CI: 0.53-1.09) and BC-specific death (HR: 0.73, 95% CI: 0.50-1.07) however, these results were not statistically significant.

[Table 3 near here]

Table 4 outlines the 5-year survival proportions for both the study and PS matched cohorts. Patients who received NAC had a 5-year survival proportion of 59%, 95% CI: 49-68% for overall and 66%, 95% CI: 56-74% for BC-specific survival in the study cohort. Similar results were found in the PS matched cohort (Table 4).

[Table 4 near here]

Further stratification by cT stage in the study cohort (Supplementary Table 2), showed only an effect on mortality for those with T2 disease (all-cause death HR: 0.62, 95% CI: 0.43-0.90 and BC-specific death HR: 0.54, 95% CI:0.35-0.81). When the PS matched cohort was stratified by cT stage, the results showed a trend towards a decrease in mortality for the T2 patients in those who had received NAC (all-cause death HR: 0.0.69, 95% CI: 0.45-1.05 and BC-specific death HR: 0.64, 95% CI:0.40-1.01), though this decrease was not significant (Supplementary Table 3).

The cumulative incidence graphs also visualise a decrease in both overall and BC-specific deaths for those who received NAC with T2 disease, when using the study cohort as well as the PS matched cohort (Supplementary Figures 1 and 2). Supplementary Figure 2 additionally shows a slight decrease in the proportion of deaths in patients with T3-T4 disease for the PS matched cohort.

Discussion

Real world data from BladderBaSe suggests that NAC prior to RC reduces the risk of both overall and BC-specific death with similar estimates of five-year survival and relative risks as previous reports of combined RCTs [19]. However, our estimates had higher variances resulting in non-statistical significant effect of NAC on survival in the PS-matched cohort.

A meta-analysis of two Nordic cystectomy trials revealed an overall survival benefit of NAC with an HR of 0.80 (95% CI: 0.64-0.99) thereby agreeing with the results from the current study [19]. This study was considered the breakthrough for NAC, and resulted in NAC being implemented into Swedish clinical practice. Many other RCTs have been carried out on this

topic with almost all concluding a survival benefit. For example, an RCT labelled BA06 30894, found that using a combination of cisplatin, methotrexate and vinblastine versus no NAC, resulted in a 16% reduction in risk of death [20]. Similarly, another trial from 2003 consisting of 317 patients, established that NAC resulted in a lower chance of residual disease being present in the cystectomy specimen as well as a significantly improved survival [5]. Subsequently, the results from these latter RCTs can be strengthened by the results from this current study [10]. RCTs which concluded no significant survival difference in patients who received NAC tended to be underpowered and often did not include the use of recommended drug combinations [2,21].

A meta-analysis initially conducted in 2003, and subsequently updated in 2005, included 11 RCTs [8,22] and revealed a significant survival benefit for patients with NAC, in particular for those receiving platinum-based, combination chemotherapy rather than a single platinum-based agent [22]. Whilst our findings are in line with this meta-analysis, unfortunately, no data on type of chemotherapy used was available in BladderBaSe. However, to our knowledge only platinum-based combinations were used in Sweden at the time.

A strength of the current study is the use of an emulated trial, as it uses real world evidence to complement the results of RCTs, whilst avoiding many types of biases including immortal time bias [23]. Even though there is a risk of selection bias, observational studies allow for a more heterogeneous population to be selected, which helps to increase the external validity of the study [24,25]. Whilst RCTs are considered gold standard for assessing the efficacy and safety of a new treatment, real world evidence can be used to identify gaps in care and to ensure the findings are tangible for the general population [10,25]. Subsequently, we utilised

the best practise from the RCT design principles, whilst exploring the heterogeneous data of BladderBaSe. This large and detailed database allowed inclusion of information such as tumour staging and CCI. Moreover, PS matching ensured that adjustment for confounding factors was separate from the analysis of the treatment effect steps [26,27]. There is always a potential for residual confounding and as some significance was lost through PS matching, it is possible that there were some residual confounders not measured or adjusted for in the conventional multivariate analysis.

The main limitation is lack of validation studies of the clinical data in the SNRUBC. It is important to highlight the potential of misclassification of clinical T stages, which can occur due to the nature of the transurethral resection of the bladder tumour (TURBT). The inexactness of clinical T staging is in part due to the lack of impact of the difference between T2 and T3 as the same treatments were considered for both. Misclassification can also be due to the classification procedure, in which there might be a substantial discrepancy between pathology reporting post-TURBT and actual clinical T stage, and in which solely the written pathology reports were used for registration. The presence or absence of hydronephrosis was not taken in account, there was an absence of registration of visual tumour size and the results of bimanual palpation were also not registered. Therefore, the results following stratification by clinical T stage must be analysed with caution. Whilst this study was conducted on an intention to treat basis, it is important to note that the misclassification of NAC treatment is also possible.

Further limitations to this study include those inherent to using retrospective data such as the lack of information regarding how NAC patients were selected. Whilst it is presumed this

would have been according to the EAU guidelines, only 30% of eligible patients received NAC. Reasons for this low uptake are not known however it may be due to the cautiousness of the clinicians in the early stages of NAC being recommended. The proportion of patients receiving NAC increased with time. Furthermore, whilst we presume most patients underwent a limited lymph node dissection, we do not have this information and therefore it is possible the results may have been influenced by this and would have ideally been adjusted for in the analyses. Finally, the use of smoking-related diseases as a proxy for smoking history is not a validated method. However, we feel this approach is more accurate than not including any smoking data at all.

Conclusion

The estimates from our emulated trial based on observational data are in line with reports from summarized RCTs but with larger statistical variability. The uncertainty in the current results may reflect a more heterogeneous effect of NAC on survival using real world data as compared to RCTs. This may be a consequence of the heterogeneity seen in observational data due to the non-randomised manner of the patient selection process. Further studies with detailed validated clinical data can be used to personalise treatment options for narrower groups of BC patients in order to maximise their chances of survival, whilst avoiding unnecessary toxicity and overtreatment.

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Legends to figures

Table 1 – Cohort characteristics for study cohort and the propensity score matched cohort

*Smoking related diseases: Chronic obstructive pulmonary disease, emphysema, bronchiolitis and respiratory conditions

CCI = Charlson comorbidity index

Table 2 - Cox-proportional hazard ratios and 95% confidence intervals for all-cause death and bladder cancer-specific death for patients who underwent radical cystectomy with or without NAC in the study cohort.

HR^a - Adjusted for smoking history, CCI, age at diagnosis, education level, marital status, gender, complications, adjuvant chemotherapy, health care region, hospital type, year of cystectomy and clinical tumour stage

* Excluding those with <1-year survival

** Excluding those who received adjuvant chemotherapy

Table 3 - Cox-proportional hazard ratios and 95% confidence intervals for overall and bladder cancer-specific death for bladder cancer patients who underwent radical cystectomy with or without NAC, in the propensity score matched cohort

HR^a - Adjusted for complications, adjuvant chemotherapy and M stage

Table 4 – 5-year survival proportions and 95% confidence intervals for overall survival and bladder cancer-specific survival in patients who underwent radical cystectomy with and without NAC.

Figure 1. Flow chart of the selection process for the study cohort from BladderBaSe. The distribution of clinical T stages is shown at each step.

Supplementary Table 1. Complications at 90 days post-radical cystectomy

Supplementary Table 2 – Stratified Cox proportional hazard analysis for overall and bladder cancer-specific death for patients who underwent radical cystectomy with or without NAC, by T stage of the tumours, in the study cohort.

HR^a - Adjusted for smoking history, CCI, age at diagnosis, education level, marital status, gender, complications, adjuvant chemotherapy, health care region, hospital type, year of

cystectomy and clinical tumour stage

** Excluding those who received adjuvant chemotherapy

Supplementary Table 3 –Stratified Cox proportional hazard analysis for overall and bladder cancer-specific death for patients who underwent radical cystectomy with or without NAC, by T stage of the tumours, in the propensity score matched cohort

HR^a - Adjusted for complications, adjuvant chemotherapy and M stage

Supplementary Figure 1. Cumulative incidence of bladder cancer-specific death and death from other causes according to T stage and neoadjuvant chemotherapy (NAC) treatment in the study cohort.

Supplementary Figure 2. Cumulative incidence of bladder cancer-specific death and death from other causes according to T stage and neoadjuvant chemotherapy (NAC) treatment when propensity score matched.